REMARKS

The present application relates to a method of treating or inhibiting the growth of cancer cells by administering certain substituted triazolopyrimidines.

Applicants request reconsideration and allowance of the application in light of the foregoing amendments and the following remarks. Entry of the amendment is requested.

Claims 2-4, 6-8, 10-12, 14-20, 22, 67, 74-77, 79-81, 83-85, 87-93 and 95-97 are pending in the application. By the current amendment claim 67 has been amended and new claim 98 has been added. Support for amended claim 67 may be found in the specification on pages 76-81 and in particular in table 1 on pages 78-81. Support for new claim 98 may be found in the specification in tables 1-6.

In the office communication of December 14, 2004 the Examiner has rejected claims 2-4, 6-8, 10-12, 14-20, 22, 67, 74-77, 79-81, 83-85, and 87-93 and 95-97 under 35 USC 112, first paragraph, because the specification, while being enabling for the treatment of lung cancer, gliobastoma, melanoma and colon cancer, does not reasonably provide enablement for the treatment of other types of cancer, or the treatment of cancerous cells that express multiple drug resistance (MDR).

Applicants respectfully traverse the rejection and provide the following table, which summarizes cell lines of human tumors used in studies presented in the specification.

Cell Line	Human Tumor Origin	Pages	Table
HeLa	Cervical	76-81	1 (pp.78-81)
COLO 205	Colon	81-95	2 (pp. 84-95)
H157	Lung	95-96	3 (p. 96)
U87MG	Brain	95-96	3 (p. 96)
PC-3 MM2	Prostate	95-96	3 (p. 96)
DLD-1	Colon	95-96	3 (p. 96)
KB, KB 8.5, KB VI	Epidermoid	97-98	4 (p. 98)
S1, S1-M1	Colon	98-99	5 (p. 99)
Reh	Acute Lymphocytic Leukemia	100-102	6 (p. 102
CCRF-CEM	Acute Lymphoblastic Leukemia	100-102	6 (p. 102)
HL-60	Promyelocytic Leukemia	101	(no table)

Applicants enable the invention by showing cell line testing data for representative examples. Support for claim breath is based on the showing and the published scientific literature where antitumor agents interacting with tubulin have been tested in further cell lines. Support found in the scientific literature for further cell lines include: Qian Cheng, et al, Bioorganic and Medicinal Chemistry Letters, 10, 517-521, (2000) ; Ke. Chen et al, J.Med.Chem. 1997, 40, 3049-3056 ; Gerald Bacher et al, Cancer Research, 61, 392-399, January 1, 2001; Richard J. Bleicher et al, Cancer Letters, 150, 129-135 (2000); H. P. Hsieh et al, Bioorganic and Chemistry Letters, 13,101-105 (2003); N. Koyanagi et al, Cancer Research, 54(7), 1702-6 (1994 April 1); Park et al, International Journal of Oncology, 20(2), 333-338 (2002); and M. Iwahana et al, Anticancer research 20(2A), 785-92 (2000 Mar-Apr). After one of ordinary skill in the art has read Applicants specification they would understand that based on their knowledge of the art that the claims are supported. The additional references from the scientific literature provided further support to those versed in the art for the breath of the coverage claimed.

Moreover, as to the rejection of claim 75 and dependent claims 74, 76, 77, 79-81, 83-85, 87-93 and 95-97, Applicants believe the claims as written comply with 35 USC 112. Applicants submit they have provided ample direction, experimental details and testing data to support the claim of a method for the treatment or prevention of cancerous tumor cells that express multiple drug resistance (MDR). Applicants have described that KB is a human epidermoid carcinoma cell line and by exposing said cell line in culture to slowly increasing concentrations of cytotoxic agents, two new cell lines KB 8.5 and KB VI are produced which show resistance not only to the cytotoxic agent used to make each cell line but also to additional cytotoxic compounds. Applicants have shown in experiments described on pages 97-99 of the specification that the basis for the resistance of said new cell lines are the expression of the drug transporter now known as P-glycoprotein (P-gp), the product of the *MDR1* gene. Together, the three cell lines (KB, KB 8.5 and KB VI) form a set which can be used to determine if a compound of the invention is a substrate of P-glycoprotein. Should the IC_{50} values of a representative compound of the invention, be determined to be about the same on KB (no P-gp expression), KB 8.5 (moderate P-gp expression) and KB VI (high P-gp expression), then the compound of the invention is not a substrate of P-gp. However, if the IC_{50} of the compound is substantially higher on KB 8.5 and KB VI than on KB, the compound of the invention is a substrate of P-gp. The IC_{50} of paclitaxel is more than 1000-

fold higher on KB VI than on KB because paclitaxel is a good substrate of P-gp. Representative examples of compounds of this invention were tested on this set of cell lines (see the specification on pages 97-98) and, as shown on page 98 of the specification in Table 4. As described and presented all of representative examples tested had essentially the same IC_{50} values on all three cell lines which indicates that the compounds are not substrates of P-gp, and therefore that they are able to overcome this form of multidrug resistance. Therefore, these data support the claim for multiple drug resistance.

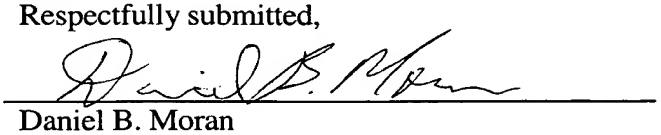
As further described in the specification (pages 98-99), similar experiments were done with the S1 human colon carcinoma cell line, and the S1-M1 cell line derived from it, which expresses another multidrug transporter called MXR. Representative examples of compounds of the invention were tested on the S1-M1 and S1 cell lines and were found to have the same IC_{50} values. The data is shown in Table 5 on pages 98-99 of the specification provide experimental evidence that the compounds are not substrates of the MXR transporter, and therefore that they are able to overcome multidrug resistance mediated by MXR. In contrast, the IC_{50} value of the clinically-used anti-cancer agent mitoxantrone was over 2000-fold higher on the S1-M1 cell line than on the S1 cell line.

The enclosed review (Trock B. J., Leonessa F., Clarke R. Multidrug resistance in breast cancer: a meta-analysis of MDR1/gp170 expression and its possible functional significance. J. Natl. Cancer Inst. (Bethesda), *89:* 917-931, 1997) critically considers the importance of P-glycoprotein (also called MDR1/gp170) in the clinical resistance of breast tumors to multiple cytotoxic agents. The authors conclude that P-gp contributes to the multidrug resistant phenotype in many breast tumors, probably in conjunction with other resistance mechanisms. Applicants believe that compounds of this invention, which are not substrates of P-gp and which are therefore active in P-gp expressing tumor cells support the claim of multidrug resistance.

Applicants believe they have complied with 35 USC 112, first paragraph and Applicants respectfully ask the Examiner to reconsider and withdraw the rejections to Claims 2-4, 6-8, 10-12, 14-20, 22, 67, 74-77, 79-81, 83-85, 87-93 and 95-97. Applicants further believe new claim 98 finding support in the specification in tables 1-6 is allowable.

Applicants respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein and amendments to the claims, and allow the application. Favorable treatment is earnestly solicited.

Respectfully submitted,



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